

Audet (10771895)

(SALONI) - COMP. SEARCH #2

=> d his nofile

(FILE 'HOME' ENTERED AT 14:48:38 ON 09 NOV 2006)

FILE 'REGISTRY' ENTERED AT 14:48:46 ON 09 NOV 2006

L1 STRUCTURE UPLOADED  
L2 2 SEA SSS SAM L1  
L3 STRUCTURE UPLOADED  
L4 STRUCTURE UPLOADED  
L5 7 SEA SSS SAM L4  
L6 2 SEA ABB=ON PLU=ON L5 AND L2  
D SCAN  
L7 56 SEA SSS FUL L4  
SAVE L7 MAURY/A TEMP

FILE 'HCAPLUS' ENTERED AT 14:54:44 ON 09 NOV 2006

E US2004-771895/APPS  
L8 2 SEA ABB=ON PLU=ON (US2004-771895/AP OR US2004-771895/PRN)  
D SCAN

FILE 'REGISTRY' ENTERED AT 14:55:25 ON 09 NOV 2006

L9 1 SEA ABB=ON PLU=ON 714394-75-9  
D SCAN  
D BROWSE  
L10 1 SEA ABB=ON PLU=ON 672305-37-2  
D SCAN  
D BROWSE  
L11 1 SEA ABB=ON PLU=ON 533881-58-2  
D SCAN  
L12 1 SEA ABB=ON PLU=ON 672305-37-2  
D SCAN  
E HUMAN GROWTH HORMONE/CN  
L13 1 SEA ABB=ON PLU=ON "HUMAN GROWTH HORMONE"/CN  
D BROWSE

FILE 'HCAPLUS' ENTERED AT 14:57:59 ON 09 NOV 2006

D SCAN L8  
SEL RN L8

FILE 'REGISTRY' ENTERED AT 14:58:38 ON 09 NOV 2006

L14 7 SEA ABB=ON PLU=ON (9002-72-6/BI OR 672305-37-2/BI OR  
25322-68-3/BI OR 533881-58-2/BI OR 714394-75-9/BI OR 721176-24-  
5/BI OR 82030-87-3/BI)  
L15 0 SEA ABB=ON PLU=ON L14 AND L7  
D RN L13  
L\*\*\* DEL 1 S 12629-01-5  
L16 0 SEA ABB=ON PLU=ON 12629-01-5/CRN  
E SOMATOTROPIN/CN  
E SOMATOTROPIN/CN  
L17 1 SEA ABB=ON PLU=ON SOMATOTROPIN/CN  
D BROWSE  
L18 8 SEA ABB=ON PLU=ON 9002-72-6/CRN  
L19 1 SEA ABB=ON PLU=ON 721176-24-5  
D SCAN  
L20 0 SEA ABB=ON PLU=ON 721176-24-5/CRN  
D BROWSE L19  
L21 1 SEA ABB=ON PLU=ON 82030-87-3  
D SCAN  
L22 12 SEA ABB=ON PLU=ON (L13 OR L17 OR L18 OR L19 OR L20 OR L21)

E E HUMAN GROWTH HORMONE/CN  
 E HUMAN GROWTH HORMONE/CN  
 L23 16 SEA ABB=ON PLU=ON ("HUMAN GROWTH HORMONE 1-43"/CN OR "HUMAN GROWTH HORMONE 172-191"/CN OR "HUMAN GROWTH HORMONE RELEASING FACTOR, HGRF(21-29)"/CN OR "HUMAN GROWTH HORMONE SEQUENCE 1-24"/CN OR "HUMAN GROWTH HORMONE SEQUENCE 122-153"/CN OR "HUMAN GROWTH HORMONE SEQUENCE 154-188"/CN OR "HUMAN GROWTH HORMONE SEQUENCE 25-51"/CN OR "HUMAN GROWTH HORMONE SEQUENCE 81-121"/CN OR "HUMAN GROWTH HORMONE(32-46)"/CN OR "HUMAN GROWTH HORMONE(6-13)"/CN OR "HUMAN GROWTH HORMONE-(177-191)"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR 1-40 AMIDE"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR(1-29) AMIDE"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR(1-40)"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR(1-40)-OH"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR(1-44)"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE (1-44) AMIDE"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE (1-29) AMIDE"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE(1-40)-OH"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE(1-44)"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE-(1-30)-AMIDE"/CN)  
 E SOMATOTROPIN/CN  
 E SOMATOTROPIN/CN  
 L24 28 SEA ABB=ON PLU=ON (L22 OR L23)  
 L25 3186 SEA ABB=ON PLU=ON (SOMATOTROPIN? OR HUMAN GROWTH HORMONE?)  
 L26 3188 SEA ABB=ON PLU=ON (L22 OR L23 OR L24 OR L25)

FILE 'HCAPLUS' ENTERED AT 15:04:40 ON 09 NOV 2006

L27 40 SEA ABB=ON PLU=ON L7  
 L\*\*\* DEL 72235 S L26  
 L28 1431 SEA ABB=ON PLU=ON HUMAN GROWTH HORMONE/CT  
 E HUMAN GROWTH HORMONE/CT  
 E E3+ALL  
 L29 1431 SEA ABB=ON PLU=ON "HUMAN GROWTH HORMONE"/CT  
 E SOMATOTROPIN/CT  
 E E3+ALL  
 E E2+ALL  
 L30 36015 SEA ABB=ON PLU=ON "GROWTH HORMONE"+RT/CT

FILE 'REGISTRY' ENTERED AT 15:05:45 ON 09 NOV 2006

E SOMATROPIN/CN  
 L31 2 SEA ABB=ON PLU=ON (SOMATROPIN/CN OR "SOMATOTROPIN, PRE-(GIRAFFA CAMELOPARDALIS)"/CN)  
 L32 3189 SEA ABB=ON PLU=ON (L26 OR L31)

FILE 'HCAPLUS' ENTERED AT 15:06:10 ON 09 NOV 2006

L33 72235 SEA ABB=ON PLU=ON L32  
 L34 18482 SEA ABB=ON PLU=ON (SOMATOTROPIN? OR HUMAN GROWTH HORMONE? OR SOMATROPIN?)/OBI,BI  
 L35 75833 SEA ABB=ON PLU=ON (L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR L34)  
 L36 8240 SEA ABB=ON PLU=ON (CORPORMON? OR CRESCORMON? OR GENOTROPIN? OR HUMAN GROWTH HORMONE? OR HUMATROP? OR INFITROPIN? OR NORDITROPIN? OR NORDOTROPIN? OR NUTROPIN? OR SAIZEN? OR SOMATOGEN? OR SR(1A)29001)/OBI,BI  
 L37 2267 SEA ABB=ON PLU=ON (VALTROPIN? OR ZOMACTON? OR ZORBTIVE? OR PHYOL? OR PHYONE? OR PITUITARY GROWTH HORMONE? OR SOMACTON? OR SOTROPIN? OR STH OR ANTERIOR PITUITARY GROWTH HORMONE? OR

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ADENOHYPOPHYSEAL GROWTH HORMONE?)/OBI,BI  
L\*\*\* DEL 76868 S L33-L37  
L38 76868 SEA ABB=ON PLU=ON (L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR  
L34 OR L35 OR L36 OR L37 OR L\*\*\*)  
L39 0 SEA ABB=ON PLU=ON L38 AND L27  
  
FILE 'REGISTRY' ENTERED AT 15:11:03 ON 09 NOV 2006  
L40 0 SEA ABB=ON PLU=ON L32 AND L7  
  
FILE 'MEDLINE, EMBASE, BIOSIS, CAOLD' ENTERED AT 15:11:53 ON 09 NOV 2006  
L41 0 SEA ABB=ON PLU=ON L7  
  
FILE 'REGISTRY' ENTERED AT 15:12:54 ON 09 NOV 2006  
  
FILE 'BEILSTEIN' ENTERED AT 15:13:37 ON 09 NOV 2006  
L42 27 SEA SSS FUL L4  
L43 26 SEA ABB=ON PLU=ON L42 NOT L7  
L44 23 SEA ABB=ON PLU=ON L42/COM  
L45 22 SEA ABB=ON PLU=ON L44 NOT L7  
  
FILE 'WPIX' ENTERED AT 15:14:27 ON 09 NOV 2006  
L46 0 SEA SSS SAM L4  
L47 0 SEA SSS FUL L4  
D QUE L4  
  
FILE 'STNGUIDE' ENTERED AT 15:17:59 ON 09 NOV 2006  
  
FILE 'REGISTRY' ENTERED AT 15:19:07 ON 09 NOV 2006  
  
FILE 'STNGUIDE' ENTERED AT 15:20:28 ON 09 NOV 2006  
  
FILE 'HCAPLUS' ENTERED AT 15:23:44 ON 09 NOV 2006  
L48 0 SEA ABB=ON PLU=ON L8 AND L27  
  
FILE 'STNGUIDE' ENTERED AT 15:24:13 ON 09 NOV 2006  
  
FILE 'REGISTRY' ENTERED AT 16:16:12 ON 09 NOV 2006  
SAVE L32 MAURYHGG/A TEMP  
  
FILE 'REGISTRY' ENTERED AT 16:23:25 ON 09 NOV 2006  
L49 STRUCTURE UPLOADED  
L50 8 SEA SSS SAM L49  
L51 204 SEA SSS FUL L49  
L52 56 SEA ABB=ON PLU=ON L51 AND L7  
  
FILE 'HCAPLUS' ENTERED AT 16:24:28 ON 09 NOV 2006  
L53 169 SEA ABB=ON PLU=ON L51  
L54 6 SEA ABB=ON PLU=ON L53 AND L38  
D KWIC  
  
FILE 'REGISTRY' ENTERED AT 16:24:58 ON 09 NOV 2006  
L55 0 SEA ABB=ON PLU=ON L51 AND L32  
  
FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 16:25:16 ON 09 NOV 2006  
L56 0 SEA ABB=ON PLU=ON L51  
  
FILE 'WPIX' ENTERED AT 16:25:25 ON 09 NOV 2006  
L57 0 SEA SSS FUL L49

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=> file hcaplus

FILE 'HCAPLUS' ENTERED AT 16:26:00 ON 09 NOV 2006  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
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FILE COVERS 1907 - 9 Nov 2006 VOL 145 ISS 20  
FILE LAST UPDATED: 8 Nov 2006 (20061108/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

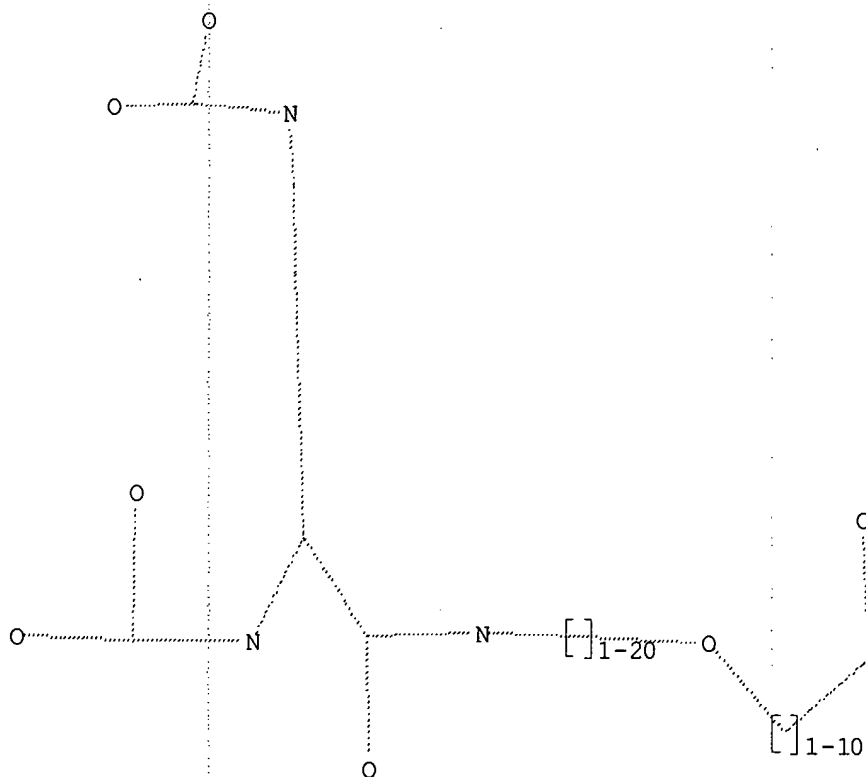
This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que 154

|     |      |                   |        |        |   |
|-----|------|-------------------|--------|--------|---|
| L13 | 1    | SEA FILE=REGISTRY | ABB=ON | PLU=ON | "HUMAN GROWTH HORMONE"/CN   |
| L17 | 1    | SEA FILE=REGISTRY | ABB=ON | PLU=ON | SOMATOTROPIN/CN   |
| L18 | 8    | SEA FILE=REGISTRY | ABB=ON | PLU=ON | 9002-72-6/CRN   |
| L19 | 1    | SEA FILE=REGISTRY | ABB=ON | PLU=ON | 721176-24-5   |
| L20 | 0    | SEA FILE=REGISTRY | ABB=ON | PLU=ON | 721176-24-5/CRN   |
| L21 | 1    | SEA FILE=REGISTRY | ABB=ON | PLU=ON | 82030-87-3  |
| L22 | 12   | SEA FILE=REGISTRY | ABB=ON | PLU=ON | (L13 OR L17 OR L18 OR L19 OR L20 OR L21)  |
| L23 | 16   | SEA FILE=REGISTRY | ABB=ON | PLU=ON | ("HUMAN GROWTH HORMONE 1-43"/CN OR "HUMAN GROWTH HORMONE 172-191"/CN OR "HUMAN GROWTH HORMONE RELEASING FACTOR, HGRF(21-29)"/CN OR "HUMAN GROWTH HORMONE SEQUENCE 1-24"/CN OR "HUMAN GROWTH HORMONE SEQUENCE 122-153"/CN OR "HUMAN GROWTH HORMONE SEQUENCE 154-188"/CN OR "HUMAN GROWTH HORMONE SEQUENCE 25-51"/CN OR "HUMAN GROWTH HORMONE SEQUENCE 81-121"/CN OR "HUMAN GROWTH HORMONE(32-46)"/CN OR "HUMAN GROWTH HORMONE(6-13)"/CN OR "HUMAN GROWTH HORMONE-(177-191)"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR 1-40 AMIDE"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR(1-29) AMIDE"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR(1-40)"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR(1-40)-OH"/CN OR "HUMAN GROWTH HORMONE-RELEASING FACTOR(1-44)"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE (1-44) AMIDE"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE(1-29) AMIDE"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE(1-40)-OH"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE(1-44)"/CN OR "HUMAN GROWTH HORMONE-RELEASING HORMONE-(1-30)-AMIDE"/CN) |
| L24 | 28   | SEA FILE=REGISTRY | ABB=ON | PLU=ON | (L22 OR L23)  |
| L25 | 3186 | SEA FILE=REGISTRY | ABB=ON | PLU=ON | (SOMATOTROPIN? OR HUMAN GROWTH HORMONE?)  |
| L26 | 3188 | SEA FILE=REGISTRY | ABB=ON | PLU=ON | (L22 OR L23 OR L24 OR L25)  |
| L28 | 1431 | SEA FILE=HCAPLUS  | ABB=ON | PLU=ON | HUMAN GROWTH HORMONE/CT   |

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L29 1431 SEA FILE=HCAPLUS ABB=ON PLU=ON "HUMAN GROWTH HORMONE"/CT  
L30 36015 SEA FILE=HCAPLUS ABB=ON PLU=ON "GROWTH HORMONE"+RT/CT  
L31 2 SEA FILE=REGISTRY ABB=ON PLU=ON (SOMATROPIN/CN OR "SOMATROTRO  
PIN, PRE- (GIRAFFA CAMELOPARDALIS)"/CN)  
L32 3189 SEA FILE=REGISTRY ABB=ON PLU=ON (L26 OR L31)  
L33 72235 SEA FILE=HCAPLUS ABB=ON PLU=ON L32  
L34 18482 SEA FILE=HCAPLUS ABB=ON PLU=ON (SOMATOTROPIN? OR HUMAN  
GROWTH HORMONE? OR SOMATROPIN?)/OBI,BI  
L35 75833 SEA FILE=HCAPLUS ABB=ON PLU=ON (L28 OR L29 OR L30 OR L31 OR  
L32 OR L33 OR L34)  
L36 8240 SEA FILE=HCAPLUS ABB=ON PLU=ON (CORPORMON? OR CRESCORMON? OR  
GENOTROPIN? OR HUMAN GROWTH HORMONE? OR HUMATROP? OR INFITROPIN  
? OR NORDITROPIN? OR NORDOTROPIN? OR NUTROPIN? OR SAIZEN? OR  
SOMATOGEN? OR SR(1A)29001)/OBI,BI  
L37 2267 SEA FILE=HCAPLUS ABB=ON PLU=ON (VALTROPIN? OR ZOMACTON? OR  
ZORBTIVE? OR PHYOL? OR PHYONE? OR PITUITARY GROWTH HORMONE? OR  
SOMACTON? OR SOTROPIN? OR STH OR ANTERIOR PITUITARY GROWTH  
HORMONE? OR ADENOHYPHYPHYSEAL GROWTH HORMONE?)/OBI,BI  
L38 76868 SEA FILE=HCAPLUS ABB=ON PLU=ON (L28 OR L29 OR L30 OR L31 OR  
L32 OR L33 OR L34 OR L35 OR L36 OR L37 OR L\*\*\*)  
L49 STR



Structure attributes must be viewed using STN Express query preparation.

L51 204 SEA FILE=REGISTRY SSS FUL L49  
L53 169 SEA FILE=HCAPLUS ABB=ON PLU=ON L51  
L54 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L53 AND L38

Audet 10771895

=> d ibib abs hitind hitstr 154 tot

L54 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:811678 HCAPLUS

DOCUMENT NUMBER: 143:235348

TITLE: Chemically-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses

INVENTOR(S): Girard, Thomas J.; Finn, Rory F.; Siegel, Ned R.

PATENT ASSIGNEE(S): Pharmacia Corporation, USA

SOURCE: PCT Int. Appl., 55 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE       |
|------------------------|--|----------|-----------------|------------|
| WO 2005075021          | A2   | 20050818 | WO 2005-IB228   | 20050131   |
| WO 2005075021          | A3   | 20060720 |                 |            |
| W:                     | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM |          |                 |            |
| RW:                    | BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG   |          |                 |            |
| CA 2553899             | AA   | 20050818 | CA 2005-2553899 | 20050131   |
| EP 1715895             | A2   | 20061102 | EP 2005-702379  | 20050131   |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU   |          |                 |            |
| PRIORITY APPLN. INFO.: |  |          | US 2004-543078P | P 20040209 |
|                        |  |          | WO 2005-IB228   | W 20050131 |

OTHER SOURCE(S): MARPAT 143:235348

AB The present invention provides a chemical modified **human Growth Hormone** (hGH) receptor antagonists, which are recombinant hGH proteins prepared by attaching a single polyethylene glycol (PEG) moiety to the N-terminus. The chemical-modified hGH receptor antagonist have decreased PEGylation heterogeneity and may also have decreased plasma residency duration, decreased clearance rate, improved stability, decreased antigenicity, increased binding affinity, increased potency or a combination thereof. The present invention relates to a method of using aldehyde chemical to direct selectivity of the PEG moiety to the N-terminus using a butyryl-aldehyde linker moiety. An embodiment of the present invention is a **human growth hormone** receptor antagonist-PEG conjugate having the structure of Formula:  $m\text{PEG-O}(\text{CH}_2\text{CH}_2\text{O})_n(\text{CH}_2)_m\text{CH}_2\text{-NH-R}$ , wherein n is an integer between 1 and 10; m is an integer between 1 and 10; R is hGH receptor antagonist. In addition, the present invention relates to pharmaceutical compns. comprising the modified hGH receptor antagonist. A further embodiment is the use of the modified hGH receptor antagonist for the treatment of growth and development disorders.

IC ICM A61P005-04  
ICS A61K047-48

CC 63-5 (Pharmaceuticals)  
Section cross-reference(s): 1, 2

ST **human growth hormone** receptor antagonist  
polyethylene glycol conjugate; **somatotropin** synthetic variant  
PEGylation therapeutic

IT Neoplasm  
(GH-responsive; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT Growth hormone receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(antagonists, conjugates; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT Drug delivery systems  
(carriers; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT **Acromegaly**  
**Growth disorders, animal**  
Human  
(chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT Polyoxyalkylenes, biological studies  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT Kidney, disease  
(diabetic nephropathy; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT Eye, disease  
(diabetic retinopathy; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT Development, mammalian postnatal  
(disorder; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT **Growth disorders, animal**  
(gigantism; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT Cell proliferation  
(inhibition; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT Protein sequences  
(of hGH receptor antagonist; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

IT 63-91-2, Phenylalanine, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(N-terminal of hGH antagonist; chemical-modified **human**

- growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)
- IT **862754-49-2D**, variants  
 RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (amino acid sequence; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)
- IT **672305-37-2DP**, conjugates  
 RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (branched chain PEG-ALD hGH antagonist; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)
- IT **218620-50-9**, B2036  
 RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)
- IT 25322-68-3, Polyethylene glycol 25322-68-3D, Polyethylene glycol, conjugates  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)
- IT 123-72-8, Butyryl-aldehyde  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (linker moiety; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)
- IT **9002-72-6, Somatotropin 9002-72-6D**, Growth hormone, conjugates  
 RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (recombinant, modified; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)
- IT **862754-49-2D**, variants  
 RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (amino acid sequence; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)
- RN 862754-49-2 HCAPLUS  
 CN Growth hormone receptor antagonist B2036 (synthetic human) (9CI) (CA INDEX NAME)

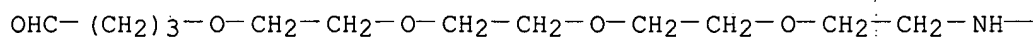
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

- IT **672305-37-2DP**, conjugates  
 RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (branched chain PEG-ALD hGH antagonist; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

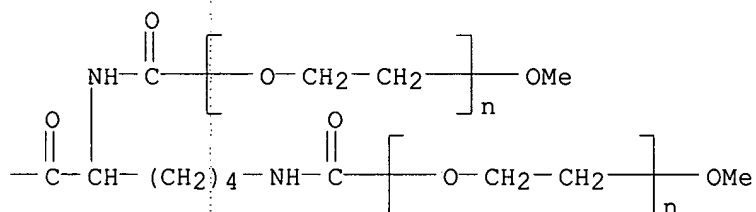
Audet 10771895

uses)  
RN 672305-37-2 HCAPLUS  
CN Poly(oxy-1,2-ethanediyl),  $\alpha,\alpha'$ -[[ (1S)-1-(1,18-dioxo-5,8,11,14-tetraoxa-2-azaooctadec-1-yl)-1,5-pentanediy]bis(iminocarbonyl)]bis[ $\omega$ -methoxy- (9CI) (CA INDEX NAME)

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PAGE 1-B



IT **218620-50-9**, B2036  
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)  
RN 218620-50-9 HCAPLUS  
CN Somatotropin [18-aspartic acid, 21-asparagine, 120-lysine, 167-asparagine, 168-alanine, 171-serine, 172-arginine, 174-serine, 179-threonine] (human), pegylated (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT **9002-72-6, Somatotropin 9002-72-6D**, Growth hormone, conjugates  
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (recombinant, modified; chemical-modified **human growth hormone** receptor (hGH) antagonist conjugates, particularly N-terminal mono-PEGylated hGH antagonist, and therapeutic uses)

RN 9002-72-6 HCAPLUS  
CN Somatotropin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 9002-72-6 HCAPLUS  
CN Somatotropin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

L54 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 2004:589444 HCAPLUS

Audet 10771895

DOCUMENT NUMBER: 141:128868  
TITLE: Polymeric reagents comprising a ketone or a related functional group  
INVENTOR(S): McManus, Samuel P.; Kozlowski, Antoni; Shen, Xiaoming; Cook, Daniel C.  
PATENT ASSIGNEE(S): Nektar Therapeutics Al, Corporation, USA  
SOURCE: PCT Int. Appl., 183 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO.  | DATE       |
|------------------------|--|----------|------------------|------------|
| WO 2004060406          | A2   | 20040722 | WO 2003-US41743  | 20031231   |
| WO 2004060406          | A3   | 20050127 |                  |            |
| W:                     | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW |          |                  |            |
| RW:                    | BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG   |          |                  |            |
| CA 2509248             | AA   | 20040722 | CA 2003-2509248  | 20031231   |
| AU 2003303519          | A1   | 20040729 | AU 2003-303519   | 20031231   |
| US 2005031576          | A1   | 20050210 | US 2003-751009   | 20031231   |
| EP 1581260             | A2   | 20051005 | EP 2003-815012   | 20031231   |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK   |          |                  |            |
| CN 1744918             | A  | 20060308 | CN 2003-80109450 | 20031231   |
| JP 2006516295          | T2   | 20060629 | JP 2004-564925   | 20031231   |
| PRIORITY APPLN. INFO.: |  |          | US 2002-437325P  | P 20021231 |
|                        |  |          | WO 2003-US41743  | W 20031231 |

AB Polymeric reagents comprising a polymer attached, either directly or through one or more atoms to a ketone or a related functional group such as ketone hydrate, thione, monothiohydrate, dithiohydrate, hemiketal, monothiohemiketal, dithiohemiketal, ketal, or dithioketal are provided. The polymeric reagents are useful for, among other things, forming polymer-active agent conjugates. Related methods, compns., preps., and so forth are also provided. For example, to 3.0 mg of lysozyme dissolved in 1 mL of 20 mM sodium phosphate buffer (pH 5.0) was added 21 mg of PEG- $\alpha$ -hydroxy- $\omega$ -2-propanone di-Et ketal (preparation given). After 15 min, 0.159 M solution of NaCNBH<sub>3</sub> was added and the solution was stirred for 20 h at room temperature. Anal. of the reaction mixture by SDS-PAGE showed that PEGylated lysozyme was formed.

IC ICM A61K047-48

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 35

IT 57-55-6, 1,2-Propanediol, reactions 78-96-6, 1-Amino-2-propanol  
97-64-3, Ethyl lactate 122-51-0, Triethyl orthoformate 123-76-2,  
Levulinic acid 617-35-6, Ethyl pyruvate 9002-68-0, FSH  
9002-72-6, Growth hormone 9004-74-4, MPEG 11096-26-7,  
Erythropoietin 37698-53-6, Amphotericin B hydrochloride 41979-39-9,  
4-Piperidone hydrochloride 61798-04-7, 1,3-Diaminoacetone  
dihydrochloride 80506-64-5 81927-55-1, Benzyl 2,2,2-

trichloroacetimidate 92451-01-9 143011-72-7, GCSF 159540-80-4  
174569-25-6

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of polymeric reagents comprising ketone or related functional group for drug conjugation)

IT 2040-44-0P 7476-20-2P 70448-03-2P, 2-Benzoyloxy-1-propanol  
84293-53-8P 104318-84-5P 161927-25-9P 161927-26-0P 175172-61-9P  
384378-74-9P 524957-45-7P 524957-46-8P 724773-68-6P 724773-69-7P  
724773-70-0P 724773-71-1P 724773-72-2P 724773-73-3P 724773-74-4P  
724773-75-5P 724773-76-6P 724773-77-7P 724773-78-8P 724773-79-9P  
724773-80-2P 724773-81-3P 724773-82-4P 724773-83-5P 724773-84-6P  
724773-85-7P 724773-86-8P 724773-88-0P 724773-90-4P 724773-91-5P  
724773-92-6P 724773-93-7P 724773-94-8P 724773-95-9P 724773-96-0P  
724773-97-1P 724773-98-2P 724773-99-3P 724774-00-9P 724774-01-0P  
724774-02-1P 724774-03-2P 724774-04-3P 724774-05-4P 724774-06-5P  
724774-07-6P 724774-08-7P 724774-09-8P 724774-10-1P 724774-11-2P  
724774-12-3P 724774-13-4P 724774-14-5P **724774-15-6P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of polymeric reagents comprising ketone or related functional group for drug conjugation)

IT 1397-89-3DP, Amphotericin B, drug conjugates 9001-63-2DP, Lysozyme,  
conjugates with PEG derivative 9002-68-0DP, FSH, conjugates with PEG  
derivative

**9002-72-6DP**, Growth hormone, conjugates with PEG derivative  
11096-26-7DP, Erythropoietin, conjugates with PEG derivative 143011-72-7DP,  
GCSF, conjugates with PEG derivative 384378-74-9DP, drug conjugates  
724773-69-7DP, conjugates with lysozyme 724773-71-1DP, conjugates with  
lysozyme 724773-72-2DP, conjugates with lysozyme 724773-73-3DP,  
conjugates with lysozyme 724773-75-5DP, drug conjugates 724773-76-6DP,  
drug conjugates 724773-77-7DP, drug conjugates

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of polymeric reagents comprising ketone or related functional group for drug conjugation)

IT **9002-72-6**, Growth hormone

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of polymeric reagents comprising ketone or related functional group for drug conjugation)

RN 9002-72-6 HCAPLUS

CN Somatotropin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

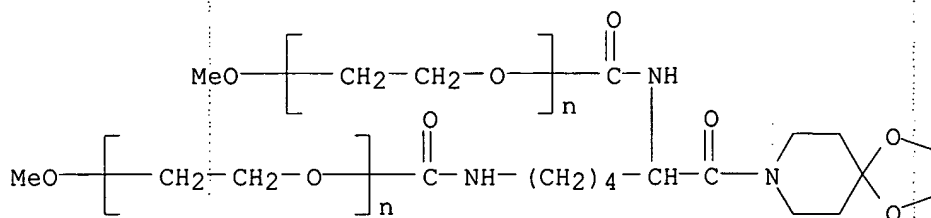
IT **724774-15-6P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of polymeric reagents comprising ketone or related functional group for drug conjugation)

RN 724774-15-6 HCAPLUS

CN Poly(oxy-1,2-ethanediyl),  $\alpha,\alpha'$ -[[ (1S)-1-(1,4-dioxo-8-azaspiro[4.5]dec-8-ylcarbonyl)-1,5-pentanediy]bis(iminocarbonyl)]bis[.omega.-methoxy- (9CI) (CA INDEX NAME)



IT **9002-72-6DP**, Growth hormone, conjugates with PEG derivative  
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of polymeric reagents comprising ketone or related functional group for drug conjugation)  
 RN 9002-72-6 HCAPLUS  
 CN Somatotropin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

L54 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 2004:533960 HCAPLUS  
 DOCUMENT NUMBER: 141:94299  
 TITLE: N-Terminally monoPEGylated **human growth hormone** conjugates and process for their preparation  
 INVENTOR(S): Finn, Rory F.  
 PATENT ASSIGNEE(S): Pharmacia Corporation, USA  
 SOURCE: U.S. Pat. Appl. Publ., 20 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

| PATENT NO.    | KIND | DATE     | APPLICATION NO. | DATE     |
|---------------|------|----------|-----------------|----------|
| US 2004127417 | A1   | 20040701 | US 2003-718340  | 20031120 |
| NL 1024831    | A1   | 20040526 | NL 2003-1024831 | 20031120 |
| NL 1024831    | C2   | 20050428 |                 |          |
| US 2004142870 | A1   | 20040722 | US 2004-771895  | 20040204 |
| NL 1028837    | A1   | 20050830 | NL 2005-1028837 | 20050421 |
| NL 1028837    | C2   | 20060814 |                 |          |

PRIORITY APPLN. INFO.: US 2002-427823P P 20021120  
 US 2003-718340 A2 20031120

AB The present invention provides a chemical modified **human Growth Hormone** (hGH) prepared by attaching a polyethylene glycol butyraldehyde moiety to the N-terminal phenylalanine of the protein. The chemical-modified protein according to the present invention may have a much longer lasting hGH activity than that of the un-modified hGH, enabling reduced dose and scheduling opportunities.

IC ICM A61K038-27  
 ICS C07K014-61

INCL 514012000; X53-039.9

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 2, 35

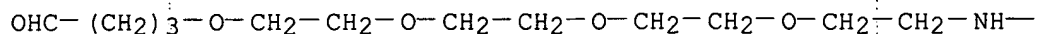
IT Kidney, disease

(failure, chronic, treatment of; preparation, pharmacokinetics, and pharmacodynamics of **human growth hormone**)

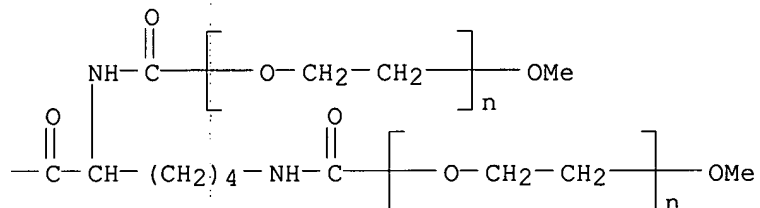
Audet 10771895

-PEG conjugates)  
IT Protein sequences  
(of **human growth hormone**; preparation,  
pharmacokinetics, and pharmacodynamics of **human  
growth hormone-PEG conjugates**)  
IT Drug bioavailability  
Drug delivery systems  
Human  
(preparation, pharmacokinetics, and pharmacodynamics of **human  
growth hormone-PEG conjugates**)  
IT Developmental disorders  
**Growth disorders, animal**  
Turner syndrome  
(treatment of; preparation, pharmacokinetics, and pharmacodynamics of  
**human growth hormone-PEG conjugates**)  
IT 714394-75-9  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**human growth hormone** sequence; preparation,  
pharmacokinetics, and pharmacodynamics of **human  
growth hormone-PEG conjugates**)  
IT 9002-72-6DP, **Somatotropin**, conjugates with PEG derivative  
82030-87-3DP, Methionyl **human growth  
hormone**, conjugates with PEG derivative 672305-37-2DP,  
conjugates with **human growth hormone**  
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP  
(Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL  
(Biological study); PREP (Preparation); USES (Uses)  
(preparation, pharmacokinetics, and pharmacodynamics of **human  
growth hormone-PEG conjugates**)  
IT 9002-72-6, **Somatotropin** 533881-58-2  
672305-37-2  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation, pharmacokinetics, and pharmacodynamics of **human  
growth hormone-PEG conjugates**)  
IT 9002-72-6DP, **Somatotropin**, conjugates with PEG derivative  
82030-87-3DP, Methionyl **human growth  
hormone**, conjugates with PEG derivative 672305-37-2DP,  
conjugates with **human growth hormone**  
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP  
(Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL  
(Biological study); PREP (Preparation); USES (Uses)  
(preparation, pharmacokinetics, and pharmacodynamics of **human  
growth hormone-PEG conjugates**)  
RN 9002-72-6 HCAPLUS  
CN Somatotropin (9CI) (CA INDEX NAME)  
  
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*  
RN 82030-87-3 HCAPLUS  
CN Somatotropin (human), N-L-methionyl- (9CI) (CA INDEX NAME)  
  
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*  
RN 672305-37-2 HCAPLUS  
CN Poly(oxy-1,2-ethanediyl),  $\alpha,\alpha'$ -[[ (1S)-1-(1,18-dioxo-5,8,11,14-  
tetraoxa-2-azaooctadec-1-yl)-1,5-pentanediy]bis(iminocarbonyl)]bis[ $\omega$ -  
methoxy- (9CI) (CA INDEX NAME)

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IT 9002-72-6, Somatotropin 672305-37-2

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation, pharmacokinetics, and pharmacodynamics of *human growth hormone*-PEG conjugates)

RN 9002-72-6 HCAPLUS

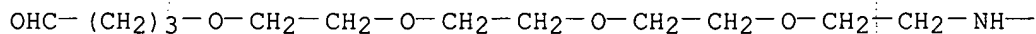
CN Somatotropin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

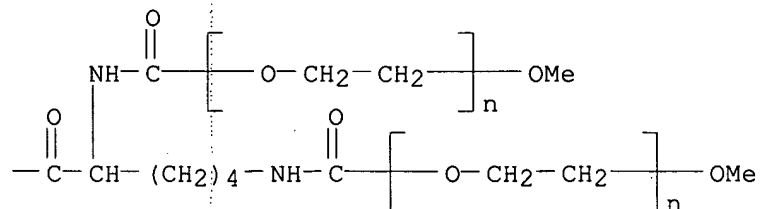
RN 672305-37-2 HCAPLUS

CN Poly(oxy-1,2-ethanediyl),  $\alpha, \alpha'$ -[[ (1S)-1-(1,18-dioxo-5,8,11,14-tetraoxa-2-azaoctadec-1-yl)-1,5-pentanediyl]bis(iminocarbonyl)]bis( $\omega$ -methoxy- (9CI) (CA INDEX NAME)

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PAGE 1-B



Audet 10771895

L54 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 2004:220384 HCAPLUS  
DOCUMENT NUMBER: 140:271415  
TITLE: Water-soluble polymer alkanals  
INVENTOR(S): Kozlowski, Antoni  
PATENT ASSIGNEE(S): Nektar Therapeutics Al, Corporation, USA  
SOURCE: PCT Int. Appl., 127 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

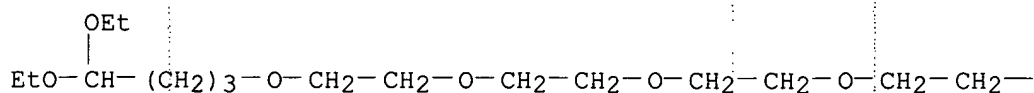
| PATENT NO.             | KIND   | DATE     | APPLICATION NO.  | DATE        |
|------------------------|--|----------|------------------|-------------|
| WO 2004022630          | A2   | 20040318 | WO 2003-US28221  | 20030909    |
| WO 2004022630          | A3   | 20040415 |                  |             |
| W:                     | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW |          |                  |             |
| RW:                    | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG   |          |                  |             |
| CA 2498167             | AA   | 20040318 | CA 2003-2498167  | 20030909    |
| AU 2003270454          | A1   | 20040329 | AU 2003-270454   | 20030909    |
| US 2004116649          | A1   | 20040617 | US 2003-659734   | 20030909    |
| EP 1546235             | A2   | 20050629 | EP 2003-752147   | 20030909    |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK   |          |                  |             |
| BR 2003014172          | A  | 20050726 | BR 2003-14172    | 20030909    |
| CN 1688631             | A  | 20051026 | CN 2003-824049   | 20030909    |
| EP 1591467             | A1   | 20051102 | EP 2005-76371    | 20030909    |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU   |          |                  |             |
| JP 2005538224          | T2   | 20051215 | JP 2004-534787   | 20030909    |
| CN 1763122             | A  | 20060426 | CN 2005-10113391 | 20030909    |
| NO 2005001077          | A  | 20050408 | NO 2005-1077     | 20050228    |
| NO 2005001078          | A  | 20050408 | NO 2005-1078     | 20050228    |
| ZA 2005002507          | A  | 20050909 | ZA 2005-2507     | 20050329    |
| AU 2005202019          | A1   | 20050602 | AU 2005-202019   | 20050511    |
| JP 2005350470          | A2   | 20051222 | JP 2005-168925   | 20050608    |
| US 2006194940          | A1   | 20060831 | US 2006-375698   | 20060313    |
| PRIORITY APPLN. INFO.: |  |          | US 2002-409251P  | P 20020909  |
|                        |  |          | US 2003-456580P  | P 20030319  |
|                        |  |          | AU 2003-270454   | A3 20030909 |
|                        |  |          | CN 2003-824049   | A3 20030909 |
|                        |  |          | EP 2003-752147   | A3 20030909 |
|                        |  |          | JP 2004-534787   | A3 20030909 |
|                        |  |          | US 2003-659734   | A1 20030909 |
|                        |  |          | WO 2003-US28221  | W 20030909  |

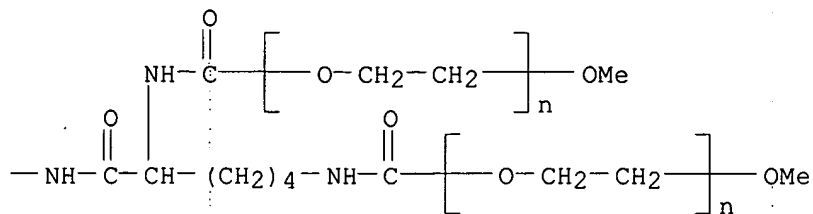
AB The present invention is directed to alkanal derivs. of water-soluble polymers such as poly(ethylene glycol), their corresponding hydrates and acetals, and to methods for preparing and using such polymer alkanals. The polymer alkanals of the invention are prepared in high purity and exhibit

storage stability. Thus, 2.0 g polyethylene glycol Me ether and 0.5 g 4-chlorobutyraldehyde di-Et acetal were reacted in the presence of 4.0 mL 1.0 M potassium tert-butoxide tert-butanol solution at 100-105° to give 1.6 g methoxy polyethylene glycol butyraldehyde di-Et acetal, 1.0 g of which was hydrolyzed to give 0.72 g methoxy polyethylene glycol butyraldehyde, which was used for pegylation of lysozyme.

- IC ICM C08G065-329  
ICS C07C047-198; C07K001-107
- CC 35-8 (Chemistry of Synthetic High Polymers)  
Section cross-reference(s): 63
- IT 38300-73-1P 63483-09-0P 177604-28-3P 533881-58-2P 672305-31-6P  
672305-32-7DP, reaction products with lysozyme 672305-32-7P  
672305-33-8P 672305-34-9P 672305-35-0P **672305-36-1P**  
672305-38-3P 672305-39-4P 672305-41-8P 672305-42-9P  
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT  
(Reactant or reagent)  
(intermediate; preparation of water-soluble polymer alkanals for pegylation  
of lysozyme)
- IT 1397-89-3DP, Amphotericin B, reaction products with methoxy  
polyoxyalkylene butyral 9001-63-2DP, Lysozyme, amino derivs., reaction  
products with methoxy polyethylene glycol butyraldehyde 9002-68-0DP,  
Follicle stimulating hormone, reaction products with methoxy  
polyoxyalkylene butyral **9002-72-6DP, Somatotropin**,  
reaction products with methoxy polyoxyalkylene butyral 11096-26-7DP,  
EPO, reaction products with methoxy polyoxyalkylene butyral  
143011-72-7DP, GCSF, reaction products with methoxy polyoxyalkylene  
butyral 533881-58-2DP, reaction products with lysozyme  
**672305-37-2P**  
RL: IMF (Industrial manufacture); PREP (Preparation)  
(preparation of water-soluble polymer alkanals for pegylation of lysozyme)
- IT **672305-36-1P**  
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT  
(Reactant or reagent)  
(intermediate; preparation of water-soluble polymer alkanals for pegylation  
of lysozyme)
- RN 672305-36-1 HCAPLUS
- CN Poly(oxy-1,2-ethanediyl),  $\alpha, \alpha'$ -[[ (1S)-1-(18-ethoxy-1-oxo-  
5,8,11,14,19-pentaoxa-2-azaheneicos-1-yl)-1,5-  
pentanediyl]bis(iminocarbonyl)]bis[ $\omega$ -methoxy- (9CI) (CA INDEX NAME)

PAGE 1-A

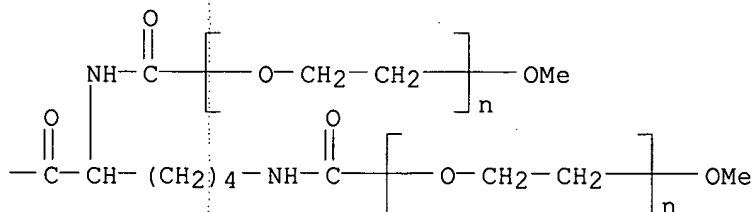
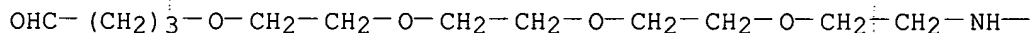




IT **9002-72-6DP, Somatotropin**, reaction products with  
 methoxy polyoxyalkylene butyral **672305-37-2P**  
 RL: IMF (Industrial manufacture); PREP (Preparation)  
 (preparation of water-soluble polymer alkanals for pegylation of lysozyme)  
 RN 9002-72-6 HCAPLUS  
 CN Somatotropin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 672305-37-2 HCAPLUS  
 CN Poly(oxy-1,2-ethanediyl),  $\alpha, \alpha'$ -[[ (1S)-1-(1,18-dioxo-5,8,11,14-tetraoxa-2-azaooctadec-1-yl)-1,5-pentanediy]bis(iminocarbonyl)]bis( $\omega$ -methoxy- (9CI) (CA INDEX NAME)



L54 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 1987:50649 HCAPLUS  
 DOCUMENT NUMBER: 106:50649  
 TITLE: GRF 1-29.  
 INVENTOR(S): Ono, Keiichi; Kai, Yoshiyuki; Takebayashi, Yoshiaki;  
 Sano, Akihiko; Suwa, Kazushi  
 PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan  
 SOURCE: Eur. Pat. Appl., 15 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English

Audet 10771895

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.                                | KIND | DATE     | APPLICATION NO. | DATE        |
|---|------|----------|-----------------|-------------|
| EP 193910                                 | A2   | 19860910 | EP 1986-102737  | 19860303    |
| EP 193910                                 | A3   | 19881123 |                 |             |
| R: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE |      |          |                 |             |
| JP 62138500                               | A2   | 19870622 | JP 1985-279682  | 19851211    |
| JP 62000099                               | A2   | 19870106 | JP 1986-46886   | 19860304    |
| US 4774319                                | A    | 19880927 | US 1987-119279  | 19871109    |
| PRIORITY APPLN. INFO.:                    |      |          | JP 1985-44370   | A 19850306  |
|   |      |          | JP 1985-279682  | A 19851211  |
|   |      |          | US 1986-832893  | A1 19860226 |

OTHER SOURCE(S): CASREACT 106:50649

GI

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-  
— Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-  
— Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH<sub>2</sub> I

AB The title compound (I) was prepared by fragment condensation in solution I was prepared from fragments 23-29, 16-22, 11-15, and 1-10.

IC ICM C07K005-00

ICS C07K007-00

ICA A61K037-02

CC 34-3 (Amino Acids, Peptides, and Proteins)

Section cross-reference(s): 2

|    |                     |              |              |              |              |
|----|---------------------|--------------|--------------|--------------|--------------|
| IT | 103339-78-2P        | 105186-96-7P | 105233-67-8P | 105233-68-9P | 105233-69-0P |
|    | 105233-70-3P        | 105233-71-4P | 105233-72-5P | 105233-75-8P | 105233-76-9P |
|    | 105233-77-0P        | 105233-78-1P | 105233-79-2P | 105233-80-5P | 105233-81-6P |
|    | 105233-82-7P        | 105233-83-8P | 105233-84-9P | 105233-85-0P | 105233-87-2P |
|    | 105233-88-3P        | 105233-89-4P | 105233-90-7P | 105233-91-8P | 105233-92-9P |
|    | 105233-93-0P        | 105233-94-1P | 105233-95-2P | 105233-96-3P | 105233-97-4P |
|    | 105233-98-5P        | 105233-99-6P | 105234-00-2P | 105234-01-3P | 105234-02-4P |
|    | 105234-03-5P        | 105234-04-6P | 105234-05-7P | 105234-06-8P | 105234-08-0P |
|    | 105234-09-1P        | 105234-10-4P | 105234-11-5P | 105234-12-6P | 105234-13-7P |
|    | 105234-14-8P        | 105234-15-9P | 105234-16-0P | 105256-56-2P |              |
|    | <b>105256-57-3P</b> | 105256-58-4P | 105256-59-5P |              |              |

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and peptide coupling of)

IT **9034-39-3P**, Growth hormone releasing factor

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of 1-29 sequence of)

IT **86168-78-7P**

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of, by fragment condensation)

IT **105256-57-3P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and peptide coupling of)

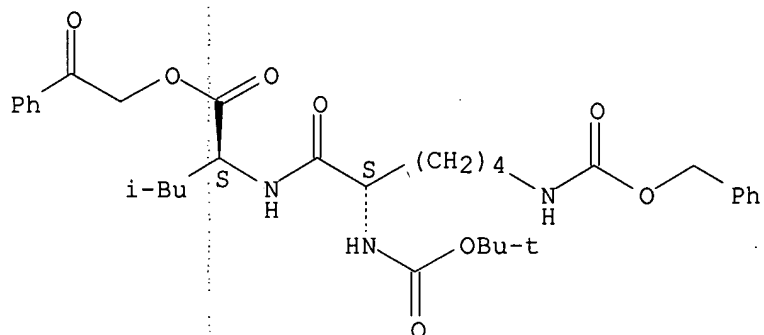
RN 105256-57-3 HCAPLUS

CN L-Leucine, N-[N2-[(1,1-dimethylethoxy)carbonyl]-N6-[(phenylmethoxy)carbonyl]-L-lysyl]-, 2-oxo-2-phenylethyl ester (9CI) (CA

Audet 10771895

INDEX NAME)

Absolute stereochemistry.

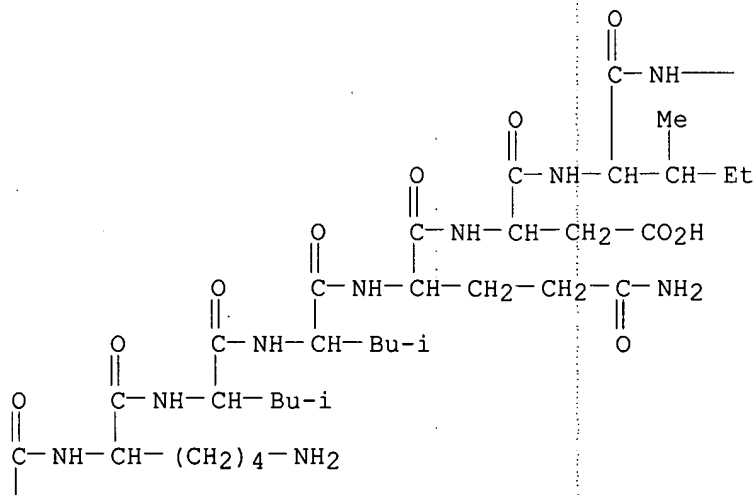


IT 9034-39-3P, Growth hormone releasing factor  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of 1-29 sequence of)  
RN 9034-39-3 HCAPLUS  
CN Somatoliberin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 86168-78-7P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of, by fragment condensation)  
RN 86168-78-7 HCAPLUS  
CN 1-29-Somatoliberin (human pancreatic islet), 29-L-argininamide- (9CI) (CA INDEX NAME)

PAGE 1-A







Audet 10771895

INVENTOR(S): Kamber, Bruno  
PATENT ASSIGNEE(S): Ciba-Geigy A.-G. , Switz.  
SOURCE: Eur. Pat. Appl., 64 pp.  
CODEN: EPXXDW  
DOCUMENT TYPE: Patent  
LANGUAGE: German  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

| PATENT NO.                                | KIND | DATE     | APPLICATION NO. | DATE       |
|---|------|----------|-----------------|------------|
| EP 83305                                  | A1   | 19830706 | EP 1982-810552  | 19821217   |
| EP 83305                                  | B1   | 19850710 |                 |            |
| R: AT, BE, CH, DE, FR, IT, LI, LU, NL, SE |      |          |                 |            |
| AT 14226                                  | E    | 19850715 | AT 1982-810552  | 19821217   |
| US 4603120                                | A    | 19860729 | US 1982-451630  | 19821220   |
| FI 8204419                                | A    | 19830625 | FI 1982-4419    | 19821222   |
| GB 2112396                                | A1   | 19830720 | GB 1982-36443   | 19821222   |
| GB 2112396                                | B2   | 19850522 |                 |            |
| ES 518453                                 | A1   | 19840601 | ES 1982-518453  | 19821222   |
| DK 8205706                                | A    | 19830625 | DK 1982-5706    | 19821223   |
| NO 8204354                                | A    | 19830627 | NO 1982-4354    | 19821223   |
| AU 8291890                                | A1   | 19830630 | AU 1982-91890   | 19821223   |
| DD 207708                                 | A5   | 19840314 | DD 1982-246477  | 19821223   |
| CA 1261548                                | A1   | 19890926 | CA 1982-418437  | 19821223   |
| JP 58116444                               | A2   | 19830711 | JP 1982-226436  | 19821224   |
| ZA 8209496                                | A    | 19831026 | ZA 1982-9496    | 19821227   |
| PRIORITY APPLN. INFO.:                    |      |          | CH 1981-8282    | A 19811224 |
|   |      |          | EP 1982-810552  | A 19821217 |

GI For diagram(s), see printed CA Issue.

AB Somatostatin analogs I [X = C4-7  $\alpha,\omega$ -diamino acid residue, X1 = Trp, D-Trp; R = H, amidino, acyl; R1 = H, amino acyl or peptidyl; Gaba = NH(CH2)3CO] were prepared as antidiabetics and agents for treating gastrointestinal bleeding (no data). Thus, Z-Lys(Boc)-Phe-Phe-OH (Z = PhCH2O2C, Boc = CO2CMe3) was coupled with H-D-Trp-Lys(Boc)-Thr(CMe3)-Phe-OTmse (Tmse = CH2CH2SiMe3) by DCC/1-hydroxybenzotriazole (HOBT) in DMF to give Z-Lys(Boc)-Phe-Phe-D-Trp-Lys(Boc)-Thr(CMe3)-Ph-OTmse, which was deblocked and then coupled with H-Gaba-OCH2Ph tosylate by DCC/HOBT in DMF containing N-ethylmorpholine to give Z-Lys(Boc)-Phe-Phe-D-Trp-Lys(Boc)-Thr(CMe3)-Phe-Gaba-OCH2Ph. The latter was deblocked by hydrogenolysis to give H-Lys(Boc)-Phe-Phe-D-Trp-Lys(Boc)-Thr(CMe3)-Phe-Gaba-OH, which was cyclized by DCC/HOBT in DMF to give a protected cyclic peptide, which was deblocked by CF3CO2H/thioglycolic acid to give cyclo(Lys-Phe-Phe-D-Thr-Lys-Thr-Phe-Gaba).

IC C07C103-52; A61K037-02

CC 34-3 (Amino Acids, Peptides, and Proteins)

Section cross-reference(s): 63

IT 87778-71-0P 87778-76-5P 87778-78-7P 87778-86-7P **87778-90-3P**  
87778-92-5P 87811-06-1P 87811-08-3P 87811-14-1P 87811-16-3P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and cleavage of (trimethylsilyl)ethyl group from)

IT 87778-73-2P 87778-80-1P **87778-88-9P** 87778-94-7P  
87811-10-7P 87811-18-5P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and hydrogenolysis of)

IT **51110-01-1DP**, cyclic octapeptide analogs  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of, by solution methods)

Audet 10771895

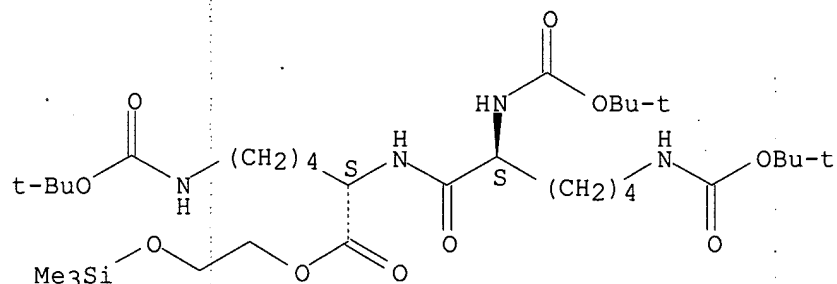
IT **87778-90-3P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and cleavage of (trimethylsilyl)ethyl group from)

RN 87778-90-3 HCAPLUS

CN L-Lysine, N2-[N2,N6-bis[(1,1-dimethylethoxy)carbonyl]-L-lysyl]-N6-[(1,1-dimethylethoxy)carbonyl]-, 2-[(trimethylsilyl)oxy]ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



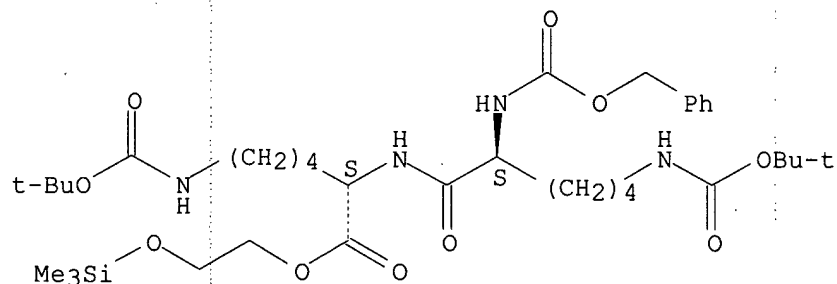
IT **87778-88-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(preparation and hydrogenolysis of)

RN 87778-88-9 HCAPLUS

CN L-Lysine, N6-[(1,1-dimethylethoxy)carbonyl]-N2-[N6-[(1,1-dimethylethoxy)carbonyl]-N2-[(phenylmethoxy)carbonyl]-L-lysyl]-, 2-[(trimethylsilyl)oxy]ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **51110-01-1DP**, cyclic octapeptide analogs

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of, by solution methods)

RN 51110-01-1 HCAPLUS

CN Somatostatin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*